

Antihistamines and allergy

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SUMMARY

There is now little role for sedating antihistamines in allergic conditions. Less sedating antihistamines are equally efficacious.

The less sedating antihistamines can be taken long term with no loss of efficacy, and an ongoing good safety profile.

Antihistamines have no role in the acute management of anaphylaxis.

Introduction

Antihistamines are used in the management of allergic conditions. They are useful for treating the itching that results from the release of histamine.

The early so-called ‘first generation’ antihistamines, such as promethazine, caused sedation. This is less of a problem with newer ‘second generation’ antihistamines, such as loratadine, and ‘third generation’ antihistamines such as desloratadine.

The oral antihistamines available in Australia to treat allergic conditions are listed in the Box. Desloratadine and fexofenadine are registered for use in infants six months and older, while loratadine and cetirizine can be used from 12 months of age. Some antihistamines are used for their antinausea or sedative properties.

Pharmacology

Antihistamines bind to histamine receptors on the surface of cells. There are four types of histamine receptors in the body (H₁–H₄), with H₁ and H₂ being most widely expressed.¹

H₁ histamine receptors are found on a variety of cells including airway and vascular smooth muscle cells, endothelial cells, epithelial cells, eosinophils and neutrophils.² Although the receptors bind histamine,

they can also signal constitutively without histamine binding to the cell surface. There is a balance between the active and inactive forms of the receptor.¹ The presence of histamine stabilises the receptor in its active form while antihistamines stabilise the inactive form of the receptor. The H₁ antihistamine drugs therefore act as inverse agonists.¹

Loratadine is metabolised in the liver, while cetirizine, desloratadine and fexofenadine are not metabolised extensively. Cetirizine is eliminated in the urine, while fexofenadine is excreted in the faeces. Dose reduction should be considered in patients with severe liver or kidney dysfunction.¹

Avoid sedating antihistamines

The sedating, first generation antihistamines now have little role in therapeutics. Their unfavourable adverse effect profile has prompted the Global Allergy and Asthma European Network to recommend making these antihistamines prescription-only, rather than over-the-counter, drugs.³ The main concerns are their sedative properties and interference with rapid eye movement sleep.^{3,4} Studies have shown poorer school performance in children with allergic rhinitis treated with sedating antihistamines, compared to children treated with non-sedating antihistamines and healthy children.⁵ Sedating antihistamines have been found to be a cause of aviation accidents.³ An audit of media reports found a number of car accidents attributed to sedating antihistamines, but none attributed to less sedating antihistamines.³

There is also concern about the use of promethazine in children less than two years old as serious behavioural and other adverse effects can occur.³ This led to a black box warning by the US Food and Drug Administration (FDA) in 2004. Sedating antihistamines can also have anticholinergic effects that can be particularly problematic in older patients who are more susceptible to adverse effects such as dry mouth, urinary retention and delirium.⁶

Box Oral antihistamines available in Australia

Sedating H ₁ antihistamines	Less sedating H ₁ antihistamines
Cyproheptadine	Cetirizine
Dexchlorpheniramine	Desloratadine
Pheniramine	Fexofenadine
Promethazine	Loratadine
Trimeprazine	

Other sedating H₁ antihistamines include doxylamine and diphenhydramine, used for sedation, and cyclizine, used mainly as an antiemetic.

Sedating antihistamines are still favoured by some, as parenteral formulations are available. However, for promethazine there is a risk of severe tissue injury, including gangrene, with both intramuscular and intravenous administration.⁷ The risk is higher for intravenous use and led to an FDA warning.⁸

The main role for sedating antihistamines is in pregnancy, where they can be used for any of the common indications for antihistamines, as they have the strongest evidence of safety. They have been taken by a large number of pregnant women and women of childbearing age without any proven increase in malformations or harm to the fetus. An exception is promethazine for which adverse events have been reported in animal studies (at very high doses). However, pregnant women must be warned about the other aspects of safety such as sedation and consider whether they should not drive while taking these drugs. The newer antihistamines are likely to be as safe in pregnancy but have not been used by as many women, so they do not have the same evidence of safety.

Newer antihistamines

The newer H₁ antihistamines are less sedating. While all the newer drugs appear equally efficacious in limited studies, there are few long-term head-to-head studies.⁹ The patient can therefore choose the particular drug that they find works best, or the formulation (tablet size) that suits them. For paediatric suspensions, the choice may be determined by a preferred flavour.

Allergic rhinitis

Allergic rhinitis refers to nasal inflammation due to the release of histamine and other mediators from IgE-mediated mast cell degranulation in the nose. Other conditions may cause similar symptoms, but they can be distinguished from allergic rhinitis by allergy testing to confirm positive allergen-specific IgE to specific triggers. Allergic rhinitis may be seasonal (usually due to grass, tree or weed pollens) or perennial (due to triggers such as pet hair, house dust mite or mould). It is important to ask the patient if they also have respiratory symptoms as a worsening in allergic rhinitis can lead to increased asthma symptoms.

Avoiding trigger factors is the first step in the management of allergic rhinitis but some triggers can be difficult to avoid. Drugs can help and oral antihistamines are one of the mainstays of treatment. They are particularly useful for nasal itchiness, sneezing and rhinorrhoea, but are less effective for nasal obstruction. Oral antihistamines also have the benefit of treating associated conjunctival symptoms.

Topical nasal antihistamines, such as azelastine, are also available and are recommended for nasal-limited mild disease and for on-demand treatment.¹⁰ To augment the efficacy of oral antihistamines in allergic rhinitis for those who continue to have symptoms, the preferred topical therapy is a corticosteroid nasal spray. These sprays should be considered first-line treatment in moderate to severe allergic rhinitis.¹⁰ Combination treatments containing both corticosteroids and antihistamines are also available. Adjunctive treatments such as intranasal ipratropium bromide may be useful in reducing rhinorrhoea in those with perennial allergic rhinitis¹¹ while nasal irrigation using saline solution may improve symptoms and reduce the need for oral antihistamines.¹²

Allergic conjunctivitis

Like allergic rhinitis, allergic conjunctivitis is IgE-mediated. It can be seasonal due to pollens or perennial due to allergens present all year.¹³ Seasonal allergic conjunctivitis is typically associated with some degree of allergic rhinitis so allergen avoidance is the first step in management.

Oral antihistamines can be used for allergic conjunctivitis or, if the symptoms are only related to the eye, topical antihistamines with or without mast cell stabilisers are recommended.¹³ Some topical products such as ketotifen, azelastine and olopatadine have both antihistamine and mast cell stabilising effects. Mast cell stabilisers such as sodium cromoglycate are also available. Topical antihistamines give immediate relief, while mast cell stabilisers provide more long-term protection.¹³

The current guidelines for ocular-limited disease are either topical antihistamines, mast cell stabilisers or dual action drugs.¹³ A Cochrane review has shown that both antihistamines and mast cell stabilisers are more effective than placebo for seasonal and perennial allergic conjunctivitis, however there have been no good studies to compare mast cell stabilisers to antihistamines.¹⁴

Acute allergic reactions

The newer H₁ antihistamines are the mainstay treatment of mild to moderate allergic reactions giving rise to allergen-specific mast cell degranulation. Patients with a known food allergy are advised to carry these less sedating H₁ antihistamines as part of their allergy action plan. The use of sedating antihistamines should be avoided, especially because their sedative effects may mask a deterioration in consciousness, caused by the underlying allergic reaction, indicating the onset of anaphylaxis and the requirement for adrenaline (epinephrine).

Antihistamines have no role in the acute treatment of anaphylaxis because intramuscular adrenaline (epinephrine) must be given. Parenteral antihistamines can potentiate hypotension and worsen anaphylaxis.¹⁵ Once the acute anaphylaxis has been treated, less sedating antihistamines and steroids may be used for symptomatic relief of urticaria.

Urticaria

In about 50% of cases, acute urticaria is not due to IgE-mediated mast cell degranulation, but occurs as a result of direct mast cell degranulation from spontaneous activation or infection. In children, the most common cause of urticaria is infection rather than IgE-mediated allergic reactions.

Irrespective of the cause of the urticaria, the less sedating antihistamines are the mainstay of the treatment. A failure of the rash to clear with these antihistamines (even if only temporarily) should prompt re-evaluation of whether the rash is truly urticarial.

Chronic spontaneous urticaria is a long-term condition of spontaneous mast cell degranulation and may occur in conjunction with various forms of physical urticaria caused by exposure to:

- water (aquagenic)
- sweat (cholinergic)
- sun (solar)
- cold
- prolonged pressure (delayed pressure urticaria).

These patients may display dermatographism. This is welting of the skin after a scratch or gentle pressure.

For patients with physical urticaria, the newer antihistamines can be used for treatment or for prophylaxis. They sometimes require up to four times the recommended dose for this treatment.

The less sedating H₁ antihistamines are also the mainstay of treatment for chronic spontaneous urticaria. This is defined by the appearance of hives at least a few times a week for more than six weeks.¹⁶ Antihistamines are most effective when dosed regularly (twice a day) to prevent the onset of hives, rather than waiting for their appearance. If required, antihistamines can be used at up to four times the recommended dose.^{16,17} If H₁ antihistamines are not effective at this dose, H₂ antihistamines such as ranitidine and famotidine (which block the H₂ receptors found in the stomach, vascular smooth muscle and elsewhere) can be added.² They are given twice a day with the same total dose as for gastroesophageal reflux. H₂ antihistamines do not help urticaria on their own, but can augment the effect of H₁ antihistamines.

Chronic spontaneous urticaria is a relapsing, remitting disease which may spontaneously improve. Patients are therefore encouraged to decrease or stop their antihistamines intermittently to ensure that the drugs are still required. Chronic spontaneous urticaria can be an autoimmune disease.¹⁷ It can also be a marker of other underlying autoimmune diseases, particularly thyroid autoimmunity, so patients should be assessed to exclude associated conditions.

Colds and flu

There is no role for antihistamines for cold and flu symptoms.

Prevention of motion sickness

Cyclizine is a sedating antihistamine used specifically for prevention of motion sickness. Other sedating antihistamines such as promethazine can also be used to treat nausea and vomiting from motion sickness.

Tachyphylaxis

There is a widespread belief in the community that taking long-term antihistamines makes them less effective and that it is better to swap between different types of antihistamines for the best effect. There is no compelling evidence that tachyphylaxis occurs with the newer H₁ antihistamines.¹ A recommendation to swap treatment is not contained in any of the position statements of the major societies which provide advice about antihistamine use. Multiple studies have shown that the effectiveness of the newer drugs in ameliorating the effect of histamine release in the skin continues unchanged for up to 30¹⁸ to 180 days.¹⁹

Patients may mistake an intensification of the underlying symptoms for a waning in effectiveness of the antihistamine. There are situations in which a pre-emptive intensification of treatment may be required – such as before contact with a known trigger or in the weeks before the onset of the spring pollen season. However, this intensification of treatment can be achieved by increased doses of the patient's usual antihistamine and does not need to involve a change to a new antihistamine that may cause idiosyncratic reactions.

Adverse effects and overdose

Newer, less sedating antihistamines have very few adverse effects. Cetirizine is the one most likely to cause sedation,²⁰ particularly in higher doses. Although very rare, idiosyncratic hypersensitivity reactions have been described for each of the antihistamines. Other reported adverse effects are headache, fatigue, drowsiness, insomnia and rash.

Sedating antihistamines have been associated with a lowered seizure threshold. Reports of seizures in patients taking less sedating antihistamines have been received by medicine safety authorities, but the causal link with the antihistamines has not been confirmed.²¹

Overdoses of newer, less sedating antihistamines may result in tachycardia, drowsiness, agitation, gastrointestinal effects and headache. An ECG is recommended. Overdoses of sedating antihistamines can give rise to dangerous sedation as well as anticholinergic signs. Seizures and cardiac conduction abnormalities may also occur.²²

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Conclusion

Antihistamines are effective at relieving the itch caused by the release of histamine. They have a role in treating allergic rhinitis, allergic conjunctivitis and urticaria. The older antihistamines caused sedation so they have now been superseded by newer, less sedating drugs. ◀

Conflict of interest: none declared



SELF-TEST QUESTIONS

True or false?

- Antihistamines are mast cell stabilisers.
- Oral antihistamines are the first-line management for allergic conjunctivitis.

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